

Conformational Energies Calculated by the Molecular Mechanics Program CHARMM

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ABSTRACT: Following the publication of a comparison of several molecular mechanics methods [Gundertofte et al., *J. Comput. Chem.* **17**, 429 (1996)], we have expanded the set of force fields tested by examining CHARMM 23.0 with its associated parameter set (version 22.0) relative to the gas-phase data used in the Gundertofte et al. study. CHARMM calculated rotational barriers and conformational energies within the same range of accuracy as the most accurate ones of the other force fields. The average absolute error was 0.64 kcal/mol, and 0.52 kcal/mol when the rotational barriers were excluded. © 1997 by John Wiley & Sons, Inc.* *J Comput Chem* **18**: 1056–1060, 1997

Recently, Gundertofte et al.¹ examined the performance of several popular molecular mechanics methods *vis-à-vis* a set of more than 40 high-quality gas-phase data. One widely used force field not included in this comparison was CHARMM (Molecular Simulations, Inc. [MSI]).² Whereas the original, “academic” version of CHARMM³ (commonly denoted by the capital final “M” versus the lower-case “m” of the “commercial” version) was, and still is to some extent, primarily geared toward biological macromolecules, in particular proteins, MSI has expanded the parameter set to allow modeling of general small organic molecules.^{4–6} It was thus of interest to

compare the newest versions of this force field and parameter set with the methods investigated by Gundertofte and coworkers.

Version 23.0 of CHARMM was used, with the version 22.0 MSI parameter set (latest revision date 92/02/17).⁷ CHARMM is usually, and was for the present study, driven by the molecular modeling program QUANTA⁸ (version 4.1.1), which provides a graphical user interface and facilitates various tasks such as model building, conformational searches, etc. All energy terms of the CHARMM force field were included. The nonbonded interactions were cut off at 15 Å, using a Shift function for the van der Waals interactions and a Force Switch function for the electrostatic interactions

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between 11 and 14 Å, the former distance being greater than the longest intramolecular distance in the molecule set. The dielectric constant was set to unity. All minimizations were performed using the Adopted-Basis Newton–Raphson⁹ algorithm until convergence, defined as an energy gradient of $\leq 0.001 \text{ kcal mol}^{-1} \text{ Å}^{-1}$, was achieved. The rotational barriers were calculated by driving the torsion under study in 1° increments and minimizing each conformer while holding that torsion fixed. The partial atomic charges, which are used in the calculation of the electrostatic part of the nonbonded interactions in CHARMM, were the template-derived charges that the 2D-Builder module of QUANTA assigns by default. Because these charges do not usually add up to zero for the set of all atoms in a molecule, a charge “smoothing” was applied which distributes a charge of equal magnitude and opposite sign among the sp^3 and aromatic carbons and the hydrogens attached to them (CHARMM atom types CT, C6R, HA).

The experimental values used in this study are the same as those given by Gundertofte et al.¹ Table I lists these energies together with the conformational energies calculated by CHARMM. In Table II, the average absolute errors are shown for all force fields as they have been reported by Gundertofte et al., with a column added for the CHARMM results.

Whereas the experimental rotational barriers were well reproduced by CHARMM in four of six cases, the calculated barriers were much too high for the methyl rotation of both propene and isoprene. For both molecules, this rotation barrier involves a torsion of the type $\text{C}_{\text{sp}2}\text{—C}_{\text{sp}2}\text{—C}_{\text{sp}3}\text{—H}$, which appears to be parameterized with too high a force constant. The other torsion in this set that represented rotation of a single bond next to a double bond between two carbons, the styrene rotation, was also somewhat overestimated in its barrier height by CHARMM. This indicates that caution should be advised when calculating non-minimum conformations of molecules containing such substructures.

The conformational energies of the hydrocarbons, oxygen compounds, and nitrogen compounds were reproduced rather well, with the discrepancies between the CHARMM results and the experimental values ($\Delta\Delta E$) being less than 1 kcal/mol for all but three molecules. For methyl acetate, $\Delta\Delta E$ was 1.1 kcal/mol, which was still better than for nine out of the other force fields. CHARMM calculated a conformational energy of 2.4 kcal/mol ($\Delta\Delta E = 1.4 \text{ kcal/mol}$) for 2-

methoxy-tetrahydropyran, which was the highest value for all force fields, but correctly identified the axial isomer to be energetically favorable, which not all force fields were able to do. The absolute average error for the subset of the nitrogen compounds (0.28 kcal/mol) was the smallest of all force fields. The cyclohexane derivatives were generally modeled accurately by CHARMM, with $\Delta\Delta E \leq 1.2 \text{ kcal/mol}$ in all cases.

While CHARMM correctly identifies the gauche conformer of 1,2-difluoroethane to be the more stable isomer, it fails to do so for two of three chloroalkanes—a shortcoming it shares with all but one of the other force fields for propyl chloride, and with some of the force fields for 1,3-dichloropropane. The conformational energies of the halocyclohexanes were generally very well reproduced, with CHARMM besting all other force fields as to the average absolute error (0.43 kcal/mol) in this subset of molecules. The only exceptions were *trans*-1,4-dichlorocyclohexane and *trans*-1,4-dibromocyclohexane, for which CHARMM erroneously calculates the equatorial positions to be the more stable ones. This error is, however, also committed by all but two of the other force fields, and CHARMM's $\Delta\Delta E$ is among the smallest with -0.9 kcal/mol and -1.28 kcal/mol , respectively. Finally, the conformational energies of the two conjugated compounds in the set were well reproduced.

The absolute average errors listed in Table II allow a comparison of CHARMM with the force fields tested by Gundertofte et al.¹ For all the individual subsets of molecules, the CHARMM results fall in the center of the distribution among the force fields, or at its top. With the exception of the rotational barriers, which were obviously affected by the two “outliers” discussed above, the average absolute errors were less than 1 kcal/mol in each of the molecule subgroups. With an average error of 0.64 kcal/mol for the whole set of compounds, and an error of 0.52 kcal/mol for all conformational energies when the rotational barriers are excluded, these results show that, in the overall picture, CHARMM approaches or matches the accuracy of the force fields based on the MM2 or MM3 functional form, which had been found to perform best among the tested force fields. It is interesting to note that among the four tested force field variants in MSI's program Cerius², which is the more recent product, only MMFF slightly surpasses the current version of CHARMM in accuracy, whereas the other force fields performed much worse. Still, room for improvement remains

TABLE I.
Conformational Energies Calculated by CHARMM (kcal / mol).

Molecule, conformational change	CHARMM	Exp. ^a
Rotational barriers		
Ethane	2.9	2.878
Propene, <i>methyl rotation</i>	4.7	1.98
Isoprene, <i>methyl rotation</i>	6.3	2.71
Ethyl benzene, <i>ethyl rotation</i>	1.6	1.7
2,4,6-Trimethyl isopropyl benzene, <i>isopropyl rotation</i>	12.0	12.8
Styrene	2.9	1.78
Hydrocarbons		
Butane, <i>gauche-anti</i>	0.8	0.97
2,3-Dimethyl butane, <i>gauche-anti</i>	0.4	0.05
1,3,5-Trineopentyl benzene, <i>twosyn-allsyn</i>	0.7	1.04
Oxygen compounds		
Methyl acetate, <i>E-Z</i>	9.1	8
2-Butanone, <i>skew-eclipsed</i>	0.2	2.0
Ethyl methyl ether, <i>gauche-anti</i>	1.5	1.5
2-Methoxy-tetrahydropyran, <i>equatorial-axial</i>	2.4	1.0
Ethanol (C—O), <i>gauche-anti</i>	0.2	0.7
Propanol (C—O), <i>gauche-anti</i>	−0.1	−0.3
Nitrogen compounds		
Ethyl amine (C—N), <i>gauche-anti</i>	0.2	0.7
<i>N</i> -Methylacetamide, <i>E-Z</i>	2.4	2.4
<i>N</i> -Methylpiperidine, <i>E-Z</i>	2.7	3.2
2-Methylpiperidine, <i>axial-equatorial</i>	2.4	2.5
3-Methylpiperidine, <i>axial-equatorial</i>	1.2	1.6
4-Methylpiperidine, <i>axial-equatorial</i>	2.1	1.93
Cyclohexanes		
Cyclohexane, <i>twistboat-chair</i>	6.7	5.5
Phenylcyclohexane, <i>axial-equatorial</i>	3.0	2.87
Methylcyclohexane, <i>axial-equatorial</i>	1.8	1.75
Aminocyclohexane, <i>axial-equatorial</i>	1.0	1.49
<i>N,N</i> -Dimethylaminocyclohexane, <i>axial-equatorial</i>	2.1	1.31
<i>trans</i> -1,2-Dimethylcyclohexane, <i>ax, ax—eq, eq</i>	2.7	2.58
<i>cis</i> -1,3-Dimethylcyclohexane, <i>ax, ax—eq, eq</i>	4.9	5.5
Haloalkanes		
FCH ₂ CH ₂ F, <i>gauche-anti</i>	−1.1	−0.8
Propyl chloride, <i>gauche-anti</i>	0.1	−0.36
ClCH ₂ CH ₂ Cl, <i>gauche-anti</i>	1.5	1.05
ClCH ₂ CH ₂ CH ₂ Cl, <i>gauche, anti—gauche, gauche</i>	−0.2	1.1
ClCH ₂ CH ₂ CH ₂ Cl, <i>anti, anti—gauche, gauche</i>	−0.2	1.5
Halocyclohexanes (only substituents listed)		
F, <i>axial-equatorial</i>	0.4	0.16
Cl, <i>axial-equatorial</i>	0.5	0.5
Br, <i>axial-equatorial</i>	0.3	0.7
<i>trans</i> -1,2-diF, <i>axial, axial—equatorial, equatorial</i>	0.8	0.59
<i>trans</i> -1,2-diCl, <i>axial, axial—equatorial, equatorial</i>	−0.9	−0.93
<i>trans</i> -1,2-diBr, <i>axial, axial—equatorial, equatorial</i>	−2.3	−1.5
<i>trans</i> -1,4-diF, <i>axial, axial—equatorial, equatorial</i>	−1.0	−1.14
<i>trans</i> -1,4-diCl, <i>axial, axial—equatorial, equatorial</i>	0.1	−0.8
<i>trans</i> -1,4-diBr, <i>axial, axial—equatorial, equatorial</i>	0.4	−0.88
Conjugated compounds		
Butadiene, <i>s-cis—s-trans</i>	2.4	2.5
Acrolein, <i>s-cis—s-trans</i>	2.5	1.7

^aSee Ref. 1.

TABLE II.
Average Absolute Errors (kcal / mol).

Package Force Field Version	MacroModel			Chem3D		Cerius ²				Alchemy		PCModel		Insight			QUANTA				
	MM2* MM3* AMBER*			"MM2"	MM2	UFF	UFF	UFF	No ch. ^a	UFF	UFF	Tripos	MMX	CFF			MM2	MM3	Blank ^b	CHARMm	23.0
	4.0	4.0	4.0											91	92	91					
Rotational barriers	0.41	1.00	1.02	1.18	1.25	1.72	2.21	1.91	0.35	2.27	1.55	1.50	0.79	1.25	0.95	3.97	1.38				
Hydrocarbons	0.14	0.36	0.48	0.14	0.14	0.56	0.30	0.65	0.39	0.57	0.29	0.42	0.24	0.35	0.12	0.69	0.28				
Oxygen compounds	0.79	0.50	0.59	0.99	1.00	3.27	2.18	1.78	0.52	1.75	0.80	1.28	0.65	0.42	1.28	2.34	0.82				
Nitrogen compounds	0.42	0.38	1.06	0.45	0.42	2.70	0.60	0.88	0.43	1.23	0.68	1.00	0.31	0.40	0.38	2.05	0.28				
Cyclohexanes	0.28	0.43	0.89	0.24	0.23	3.71	1.44	1.15	0.71	0.80	0.22	2.60	0.71	0.34	0.21	3.00	0.49				
Haloalkanes	0.59	0.72	1.07	0.76	0.79	2.70	1.32	1.31	0.39	0.97	0.82	2.09	2.02	0.80	0.76	0.96	0.84				
Halocyclohexanes	0.72	0.69	0.93	0.53	0.55	4.57	1.78	1.26	0.68	1.05	0.53	3.13	2.36	0.69	0.54	0.80	0.43				
Conjugated compounds	0.15	0.46	0.70	0.11	0.08	2.11	0.79	0.80	0.19	1.42	0.30	0.98	0.08	0.40	0.15	2.10	0.44				
Total	0.50	0.60	0.88	0.60	0.62	3.01	1.48	1.29	0.51	1.27	0.68	1.88	1.08	0.61	0.60	2.03	0.64				
Excluding rotational barriers	0.51	0.53	0.86	0.51	0.52	3.22	1.36	1.20	0.53	1.11	0.55	1.94	1.13	0.51	0.55	1.73	0.52				

^a UFF 1.01 with all charges set to zero.
^b Errors that would result from setting all energy differences to 0 kcal / mol.

in CHARMM, too, as individual results of this study show.

Note Added in Proof

For additional recent publications discussing conformational energies calculated by various molecular mechanics methods as well as experimental data, see the studies by Pettersson and Liljefors,¹⁰ and by Halgren.¹¹

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